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WARNER LAMBERT

September 14, 1999

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products (HFD-560)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Building Two
Rockville, MD 20850

Attention: Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Subject: **Pre-meeting Materials for October 8, 1999 Feedback Meeting.**

Docket No. 80N-0042.
"Anticaries Drug Products for Over-the-Counter Human Use; Final Monograph," 60(194) *Federal Register* 52474-52510, October 6, 1995.

Docket No. 81N-0033.
"Over-the-Counter Dental and Oral Health Care Drug Products for Antiplaque Use; Safety and Efficacy Review," 55(182) *Federal Register* 38560-38562, September 19, 1990.

Dear Dr. Ganley:

Thank you for the upcoming feedback meeting on Friday, October 8, 1999. The purpose of the meeting is to discuss the process to harmonize dosing for an over-the-counter combination drug product. The drug products we will discuss are anticaries oral rinses, which are covered by a final rule[1], and

[1] "Anticaries Drug Products for Over-the-Counter Human Use," 21 CFR § 355. For convenience, the rule is presented as Attachment 1.
"Anticaries Drug Products for Over-the-Counter Human Use; Final Monograph," 60(194) Federal Register 52474-52510, October 6, 1995.

81N-0033

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antiplaque/antigingivitis oral rinses, which are subject to an ongoing rulemaking process.[2]

The specific issue we will discuss follows.

We wish to discuss the regulatory process to harmonize dosing between two product monographs. We seek agreement on October 8 on a regulatory process that will permit interim marketing of a combination drug product providing anticaries and antiplaque/antigingivitis benefits on the basis of a feedback meeting after successful completion of appropriate studies and review and acceptance of a citizen petition submitted to the Agency.

This approach is consistent with previous Agency actions and is discussed in greater detail below. If the Agency agrees with the proposed regulatory pathway, we seek a letter stating the Agency's concurrence before we initiate a clinical program.

Also, if the Agency believes that the argument presented below is clear and convincing, we propose that the October 8 meeting may not be necessary. We will waive the request for the meeting with the Agency's commitment to promptly send a feedback letter agreeing to the proposed regulatory pathway.

We recognize that we will subsequently submit a clinical program that will be the bases of a citizen petition to amend the anticaries monograph. We will promptly submit a clinical study that will be the basis of a citizen petition to amend the monograph, and we will request a meeting to gain Agency agreement on our clinical program. We do not wish to discuss the study needed to amend the anticaries final rule on October 8.

Background

Listerine® Mouthwash is an antiplaque and antigingivitis oral healthcare drug product marketed by Warner-Lambert Company. Warner-Lambert has submitted information on the active ingredients in Listerine Mouthwash to the agency in response to a "call-for-data."[3] An independent advisory committee of experts at the agency's invitation has reviewed this material and unanimously recommended that the active ingredients in Listerine Mouthwash are generally recognized as safe and effective in the control of plaque and gingivitis. They

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2 "Over-the-Counter Dental and Oral Health Care Drug Products for Antiplaque Use; Safety and Efficacy Review," 55(182) *Federal Register* 38560-38562, September 19, 1990. For convenience, this *Federal Register* citation is presented as Attachment 2.

3 Supra note 2.

recommended the ingredients be placed in Category I.[4] The dosage and instructions for antiplaque and antigingivitis use are to rinse with 20 mL for thirty seconds twice daily.

The panel further recommended that a product formulated to provide both anticaries and antigingivitis benefits is a rational combination.

The final rule for anticaries drug products contains several ingredients that can be formulated into treatment rinses.[5] The directions for these treatment rinses instruct one to rinse with 10 milliliters for sixty seconds either once or twice daily, depending on ingredient and concentration.[6] Therefore, there is a discrepancy between directions recommended for safe and effective use of treatment rinses formulated for anticaries and antiplaque/antigingivitis use.[7]

Regulatory Considerations

We have an interest in developing and marketing a product with antigingivitis and anticaries claims. An oral rinse product offering gingivitis and caries prevention represents a significant advancement in oral care and has been recommended as Category I by the plaque and gingivitis advisory panel.

The anticaries rulemaking has concluded with the publication of the final rule for these products. Therefore, we wish to determine a mutually agreeable regulatory pathway that will enable marketing a combination antigingivitis and anticaries mouthwash with dosing different from that set forth in the anticaries monograph.

We trust that we can reach an agreement on a regulatory pathway at the October 8 meeting. We will then meet with FDA medical personnel to obtain agreement on the study needed to support a change in the anticaries monograph to provide for an alternate-dosing regimen. Once the study is successfully completed, we will submit a citizen petition to amend the anticaries monograph to add the alternate-dosing regimen. The petition will also request that FDA allow the combination product to be marketed with the alternate anticaries dosing regimen following Agency feedback and during the pendency of the petition.

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4 Transcript of the Dental Plaque Subcommittee Meeting, Nonprescription Drugs Advisory Committee, Center for Drug Evaluation and Research, Food and Drug Administration., Oct 29-30, 1997, pages 173-174.

5 Supra note 1, at § 355.10.

6 Supra note 1, at § 355.50(d).

7 For convenience, a table presenting ingredients and directions is presented as Attachment 3. This dosing discrepancy was not observed with dentifrice dosage forms. Toothpastes have a customary pattern of use. They are generally recommended for use twice-a-day, and the application device (i.e., toothbrush) limits the amount delivered to approximately one gram.

Both the law and FDA precedent support the proposed regulatory path. FDA has the administrative discretion to withhold enforcement in the interest of public health,[8] and examples of explicit nonenforcement decisions permitting interim marketing are plentiful under the OTC Drug Review.

For instance, the anticaries final monograph does not permit the combination of fluoride with any other active ingredient. Yet, FDA issued an enforcement policy permitting the marketing of a toothpaste containing a combination of an approved fluoride ingredient and potassium nitrate with claims of cavity prevention and tooth desensitization, pending establishment of final monographs for both anticaries and oral health care drug products in 1992.[9] No advisory panel had considered the combination in question.

As another example, FDA announced in 1997 that it would exercise its enforcement discretion to allow over-the-counter marketing of sunscreen products containing avobenzone alone and in combination with certain approved sunscreen ingredients. Again, no panel had considered avobenzone or avobenzone-containing combination drug products, and marketing of such products prior to a final monograph would have been subject to regulatory action. Marketing of avobenzone sunscreens was permitted pending establishment under the OTC Drug Review of a final monograph covering sunscreen products.[10]

There are numerous other examples, both within the OTC Drug Review context and outside that context, of instances where FDA has exercised its administrative discretion to withhold enforcement in the FD&C Act or its regulations when it is in the public interest. For example, FDA also implemented enforcement policies

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8 See, for example, "Marketing Status of Ingredients Recommended for Over-the-Counter Use; Amendment to Enforcement Policy," 47 *Federal Register* 17738 – 739, April 3, 1982.
For convenience, this notice is submitted as Appendix 4.

9 "Combination Drug Products Containing Potassium Nitrate and an Anticaries Ingredient; Marketing Status for Over-the-Counter Human Use; Notice of Enforcement Policy," 57 *Federal Register* 20114 – 20115, May 11, 1982.
"Oral Health Care Drug Products for Over-the-Counter Human Use; Amendment to Tentative Final Monograph to Include OTC Relief of Oral Discomfort Drug Products," 56 *Federal Register* 48302 – 4837, September 24, 1991, at 48330 – 48332.
For convenience, both these references are provided as Appendix 5.

10 "Sunscreen Drug Products for Over-the-Counter Human Use; Marketing Status of Products Containing Avobenzone; Enforcement Policy," 62 *Federal Register* 23350 – 23356, April 30, 1997.
"Sunscreen Drug Products for Over-the-Counter Human Use; Amendment to Tentative Final Monograph," 61 *Federal Register* 48645 – 48655, September 16, 1996.
For both these references are provided as Appendix 6.

consistent with the two examples cited above for cough/cold products,[11] antacids,[12] external analgesics,[13] and nighttime sleep-aid[14] drug products.

In summary, FDA has the discretion to adopt creative solutions to problems such as this one, and we wish to work closely with the agency to address the dosing discrepancy identified between two OTC monographs.

We commit to promptly develop a protocol for a human clinical study, which, if successful, will be the basis for a petition to amend the anticaries monograph. As previously stated, we do not wish to discuss the design of the appropriate clinical study at the October 8 meeting. Rather, we will submit the clinical package for agency review promptly after we have agreed to the regulatory pathway discussed above.

If you have any questions or would like any additional information in advance of the feedback meeting, please contact Paul Okarma, Ph.D., Director, Regulatory Affairs, directly. His direct-dial telephone number is (973) 385-5031.

We look forward to a productive meeting.

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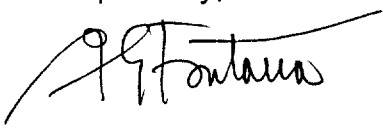
11 "Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Products Containing Diphenhydramine Citrate or Diphenhydramine Hydrochloride; Enforcement Policy, Final Rule," 61 *Federal Register*, 15700 – 003, April 5, 1996.
For convenience, this reference is provided as Appendix 7.

12 "Antacid and Acetaminophen Combination Drug Products in a Solid Dosage Form; Marketing Status for Over-the-Counter Human Use; Notice of Enforcement Policy," 57 *Federal Register* 4456 – 457, February 5, 1992.
For convenience, this reference is provided as Appendix 8

13 "Hydrocortisone; Marketing Status as an External Analgesic Drug Product for Over-the-Counter Human Use,""56 *Federal Register* 43025 – 026, August 30, 1991.
For convenience, this reference is provided as Appendix 9.

14 "Nighttime Sleep-Aid Drug Products for Over-the-Counter Human Use; Final Monograph," 54 *Federal Register* 6814 – 827, February 14, 1989.
"Diphenhydramine; Notice of Enforcement Policy; Marketing Status as an OTC Nighttime Sleep-Aid Drug Product," 47 *Federal Register* 17740 – 741, April 23, 1982.
"Diphendydramine – Marketing Status as a Nighttime Sleep-Aid Drug Product," OTC Drug Study Bulletin Number 14, May 5, 1982.
For convenience, this reference is provided as Appendix 10.

Respectfully,



for Judith M. Sills, Pharm.D.
Senior Director
U.S. Regulatory Affairs
and Global Product Safety

JMS:pjo

Attachments

Desk copies (12) to
Mr. Kerry Rothschild, HFD-560

Appendices

Appendix 1 "Anticaries Drug Products for Over-the-Counter Human Use," 21 CFR § 355.

Appendix 2 "Over-the-Counter Dental and Oral Health Care Drug Products for Antiplaque Use; Safety and Efficacy Review," 55(182) *Federal Register* 38560-38562, September 19, 1990.

Appendix 3 Active Ingredients and Directions for Use of Anticaries Drug Products. Treatment Rinses.

Appendix 4 "Marketing Status of Ingredients Recommended for Over-the-Counter Use; Amendment to Enforcement Policy," 47 *Federal Register* 17738 – 739, April 3, 1982.

Appendix 5 "Combination Drug Products Containing Potassium Nitrate and an Anticaries Ingredient; Marketing Status for Over-the-Counter Human Use; Notice of Enforcement Policy," 57 *Federal Register* 20114 – 20115,May 11, 1982.

"Oral Health Care Drug Products for Over-the-Counter Human Use; Amendment to Tentative Final Monograph to Include OTC Relief of Oral Discomfort Drug Products," 56 *Federal Register* 48302 – 4837, September 24, 1991, at 48330 – 48332.

Appendix 6 "Sunscreen Drug Products for Over-the-Counter Human Use; Marketing Status of Products Containing Avobenzone; Enforcement Policy," 62 *Federal Register* 23350 – 23356, April 30, 1997.

"Sunscreen Drug Products for Over-the-Counter Human Use; Amendment to Tentative Final Monograph," 61 *Federal Register* 48645 – 48655, September 16, 1996.

Appendix 7 "Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Products Containing Diphenhydramine Citrate or Diphenhydramine Hydrochloride; Enforcement Policy, Final Rule," 61 *Federal Register*, 15700 – 003, April 5, 1996.

Appendix 8 "Antacid and Acetaminophen Combination Drug Products in a Solid Dosage Form; Marketing Status for Over-the-Counter Human Use; Notice of Enforcement Policy," 57 *Federal Register* 4456 – 457, February 5, 1992.

Appendix 9 "Hydrocortisone; Marketing Status as an External Analgesic Drug Product for Over-the-Counter Human Use," 56 *Federal Register* 43025 – 026, August 30, 1991.

Appendix 10 "Nighttime Sleep-Aid Drug Products for Over-the-Counter Human Use; Final Monograph," 54 *Federal Register* 6814 – 827, February 14, 1989.

"Diphenhydramine; Notice of Enforcement Policy; Marketing Status as an OTC Nighttime Sleep-Aid Drug Product," 47 *Federal Register* 17740 – 741, April 23, 1982.

"Diphendydramine – Marketing Status as a Nighttime Sleep-Aid Drug Product," OTC Drug Study Bulletin Number 14, May 5, 1982.